GE Healthcare

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To	Examiner Sue Liu
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Date	June 22, 2009
Number of pages including this one	8

Dear Examiner Liu:

Thanks again for granting an Examiner's Interview for **US 10/621,495 (PA0248)** this Wednesday, June 24, 2009 at 10:00 a.m.

Please find some material we prepared that we hope would help our discussion:
(1) A one page discussion of the invention entitled "Functional Screening Method";
(2) A discussion of the 35 USC 103(a) rejection; and
(3) Proposed claims amendment, in which we propose to amend claims 1 and 2 extensively.

Currently, three people plan to join the call:
Yonggang Ji (US), Ian Bryan (UK) and Nick Thomas(UK).

The telephone conference details are as follows:
T-Con dial-in number: 1.800.747.1631
Access Code: 3312789

Kind regards:
Yonggang Ji

Functional Screening Method

Consider a first case: a cell expresses an indicator protein where the indicator protein is resident in the cytoplasm (C). Treatment with a chemical modulator (A) causes translocation of the indicator to the nucleus. Treatment with an effector nucleic acid sequence (B) simultaneously with the modulator causes the indicator to remain in the cytoplasm; i.e. the effector antagonises the function of the modulator. This may be expressed as;

$$A + B = C$$

such that if a second effector (X) is substituted with the same result;

$$A + X = C$$

then a functional equivalence may be inferred;

$$X \equiv B$$

The biological activity and/or function of any or all of A, B or C may be known or unknown (i.e. fully characterised, partially characterised or uncharacterised). If the functions of A, B and C are known then X can be inferred to be functionally equivalent to B. If the functions of A and C are unknown but the function of B is known then X may still be inferred to be functionally equivalent to B. If the functions of A, B and C are all unknown the function of X may not be inferred, however an equivalence linkage is established;

$$[A + B = C] \equiv [A + X = C]$$

which may be used in conjunction with further groupings of indicators, modulators and effectors of known and unknown function to establish functional equivalences. By extension, if the above components are extended to include a third effector (Z) of known function with the result;

$$[A + B = C] = [A + X = C] = [A + Z = C]$$

then the functions of both effectors X and B can now be inferred from the known function of Z.

Consider a second case: a cell expresses an indicator protein where the indicator protein is resident in the cytoplasm (C). Treatment with a chemical modulator (D) causes translocation of the indicator to the nucleus. Treatment with a second modulator (A) causes the indicator to revert to the cytoplasm (A antagonises D). Treatment with an effector nucleic acid sequence (B) simultaneously with the modulators causes translocation of the indicator to the nucleus (B antagonises A. This may be expressed as;

$$A + B = C + D$$

as described for the first case, if a second effector (X) is substituted with the same result;

$$A + X = C + D$$

then a functional equivalence may be inferred;

$$X = B$$

As above, if the functions of A, B, C and D are all unknown the function of X may not be inferred, however an equivalence linkage is established;

$$[A + B = C + D] = [A + X = C + D]$$

allowing further linkage to groupings containing components of known function as described above and thereby assigning function to components of previously unknown function.

PA0248 US: Proposed Response to Claim rejection based on 35 USC 103(a)

Thastrup WO98/45704 cited by the examiner teaches use of imaging to measure changes in the distribution of a luminophore, specifically GFP, within cells where the GFP is fused to a protein of known function, wherein changes in distribution of the fusion protein provides information relating to an external influence, specifically a substance having biological activity, on a cell response.

Consequently Thastrup teaches a screening method for determining the activity of a substance, typically a candidate drug, against a known biological process using a GFP fusion to a DNA sequence coding for a protein of known function.

Thastrup teaches the use of only two components;

(i) a GFP fusion protein (e.g. PKA-GFP); which is the equivalent of the indicator in the present invention
(ii) a test substance (e.g. forskolin); which is the equivalent of the modulator in the present invention

The method of Thastrup provides means to determine whether a substance having biological activity is active against a chosen known cellular process, e.g. to determine if a drug candidate compound inhibits a cellular signalling pathway which is the focus of a therapeutic program. In this aspect the method of Thastrup conforms to standard drug screening methodology, i.e. providing an assay against which multiple compounds may be individually tested in parallel for activity.

Since the method of Thastrup utilises only two components, the function of one of which by definition has to be known, the method does not teach or motivate the method of the present invention in providing means to generate networks of functional linkages using combinations of indicators, modulators and effectors of both known and unknown function in order to assign function.

Since Thastrup does not teach or motivate the method of the present invention, addition of the teachings of Bastiaens, Rolls or Diamond which relate only to the use of GFP fusion proteins to measure cellular events (as described by Thastrup) and to the use of chemical libraries for drug screening (as described by Thastrup) is redundant.

PA0248: Proposed claim amendments:

Claim 1 (currently amended): A method for determining the function ~~or effect of an~~ of one or more effector nucleic acid ~~sequence~~ sequences from a library of effector nucleic acid sequences ~~or a chemical modulator from a library of chemical modulators of known and unknown function on a population of cells~~ comprising:

i) determining the distribution of a detectable label expressed from one of a group of ~~an~~ indicator nucleic acid sequences expressed ~~sequence~~ in ~~said~~ cells in both the presence and ~~or~~ the absence of one of a ~~first~~ group of chemical modulators ~~modulator,~~ which affect ~~modulator affects~~ said distribution of said detectable label, wherein the cells express one of said ~~are both co-expressing said library of~~ effector nucleic acid sequences; ~~and are in the presence of said library of second chemical modulators; and~~

ii) repeat step i) with a different effector nucleic acid sequence from said library of effector nucleic acid sequences;

iii) analyzing ~~analyzing~~ the distribution data of said detectable label from all combinations of said ~~effector~~ effectors, modulator and indicator to derive functional linkages among said effectors, modulator and indicator; and ~~assign function to the effector and said second modulator~~

iv) repeating steps i) to iii) with different combinations of effector nucleic acid sequences, chemical modulators and indicator nucleic acid sequences until a function is assigned successfully to said one or more effector nucleic acid sequences.

Claim 2 (currently amended): A method for determining the function ~~or effect~~ of one or more ~~an~~ effector nucleic acid sequences ~~sequence~~ from a library of effector nucleic acid sequences ~~or a chemical modulator from a library of chemical modulators of known and unknown function on a population of cells~~ comprising:

i) determining the distribution of a detectable label expressed from one of a group of ~~an~~ indicator nucleic acid sequences expressed ~~sequence~~ in ~~said~~ cells in the presence of ~~a first~~ one of a group of chemical modulators ~~modulator,~~ which ~~modulator affects~~ affect said distribution of said detectable label, wherein the cells express one of said ~~are both co-expressing said library of~~ effector nucleic acid sequences ~~and are in the presence of said library of second chemical modulators~~;

ii) comparing the distribution data of i) above with known distribution data, stored on an electronic or optical database, for the detectable label in the absence of said ~~first~~ chemical modulator; ~~and~~

iii) repeating steps i) and ii) with a different effector nucleic acid sequence from said library of effector nucleic acid sequences; and

iv) analyzing ~~analyzing~~ the distribution data of said detectable label from all combinations of said ~~effector~~ effectors, modulator and indicator to derive functional linkages among said effectors, modulator and indicator; and ~~ssign function to the effector and said second modulator~~

v) repeating steps i) to iv) with different combinations of effector nucleic acid sequences, chemical modulators and indicator nucleic acid sequences until a function is assigned successfully to said one or more effector nucleic acid sequences.

Claim 3 (currently amended): The method of claim 1, wherein each of the effector nucleic acid sequences ~~sequence~~ encodes a protein or peptide and is selected from the group consisting of DNA, cDNA, RNA and Protein Nucleic Acid.

Claim 4 (currently amended): The method of claim 1, wherein each of the effector nucleic acid sequences is an antisense oligonucleotide.

Claim 5 (withdrawn, currently amended): The method of claim 1, wherein each of the effector nucleic acid sequences is a small interfering RNA (siRNA) which causes gene silencing.

Claim 6 (currently amended): The method of claim 1, wherein each of the effector nucleic acid sequences includes a nucleic acid sequence in a cellular expression vector.

Claim 7 (original): The method of claim 6, wherein said expression vector is selected from the group consisting of plasmid, retrovirus and adenovirus.

Claim 8 (cancelled)

Claim 9 (currently amended): The method of claim 1, wherein each ~~the~~ indicator nucleic acid sequence is created by fusing the effector nucleic acid sequence to a nucleic acid sequence encoding a detectable label.

Claim 10 (previously presented): The method of claim 1, wherein said detectable label is selected from the group consisting of fluorescent proteins, enzymes, antigens and antibodies.

Claim 11 (currently amended): The method of claim 10, wherein said fluorescent proteins are ~~protein is a~~ modified Green Fluorescent Proteins ~~Protein~~ (GFP) having one or more mutations selected from the group consisting of Y66H, Y66W, Y66F, S65T, S65A, V68L, Q69K, Q69M, S72A, T203I, E222G, V163A, I167T, S175G, F99S, M153T, V163A, F64L, Y145F, N149K, T203Y, T203Y, T203H, S202F and L236R.

Claim 12 (previously presented): The method of claim 11, wherein said modified GFP has three mutations selected from the group consisting of F64L-V163A-E222G, F64L-S175G-E222G, F64L-S65T-S175G and F64L-S65T-V163.

Claim 13 (withdrawn, currently amended): The method of claim 10, wherein said enzymes are ~~enzyme is~~ selected from the group consisting of β-galactosidase, nitroreductase, alkaline phosphatase and β-lactamase.

Claim 14-15 (cancelled)

Claim 16 (currently amended): The method of claim 1, wherein said cells are ~~cell is an~~ eukaryotic cells ~~cell~~.

Claim 17 (currently amended): The method of claim 16, wherein said eukaryotic cells are ~~cell is~~ selected from the group consisting of mammal, plant, bird, fungus, fish and nematode cells, which cells ~~cell~~ may or may not be genetically modified.

Claim 18 (currently amended): The method of claim 17, wherein said mammalian cells are human cells ~~cell is a human cell~~.

Claim 19 (previously presented): The method of claim 1, wherein the distribution of the detectable label is determined using an imaging system.

Claim 20 (cancelled)